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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,905	03/23/2004	David Scheinberg	D6499	2406

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,905	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,8-12,49,51-53 and 58-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-5, 8-12, 49, 51-53 and 58-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/06/2008 has been entered.

Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-63 are currently pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-5, 8-12 and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, claim 1 recites a method of reducing the nephrotoxicity in an individual during radioimmunotherapeutic treatment of a pathological condition comprising: administering a pharmacologically effective dose of one or more diruetics and a chelated actinium-225 radioimmunoconjugate, wherein interaction between said diuretics prevents accumulation of francium 221 and bismuth 213 daughters in the kidneys. As such, it is unclear whether the diuretics interact with themselves or with the francium 221 and bismuth 213.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-5, 8, 10-11, 49, 51-53, 59-60 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731, of record), Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*), and Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) in further view of Nair et al. (J. Radiat. Res. 2001; 42: 21-37, of record).

Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate (abstract). The reference further teaches that while the isotope coupled to the targeting monoclonal antibody delivers a tumorcidal dose to the lung, the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy (page 242, 2nd column, last paragraph). For example, Kennel et al. teach at necropsy, animals had total ablation of bone marrow cells, splenic atrophy, some damage to the lining of their stomachs and intestine and excess accumulation of undigested food in their stomachs (page 240, 1st column, paragraph bridging page 239).

Kennel et al. do not explicitly teach administering a competitive metal blocker such as bismuth subnitrate, a chelator such as DMPS or a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ–ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage by γ-ray irradiation without compromising the tumor-reducing effect (page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from

radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Nair et al. teach radioprotector in radiotherapy. In particular, the reference teaches that while acute toxicity has been a main reason for radioprotectors failure in clinical applications, the use of nontoxic amounts of several radioprotectors having a different mechanism of action can overcome the problems associated with their toxicity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention to combine the teachings of the references so as to modify the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al.. One would have been motivated to do so because each of the references teach that the agents are effective at reducing toxicities associated with radiotherapies. Moreover, as taught by Nair et al., combining several radioprotectors having a different mechanism of action can overcome problems associated with radioprotector toxicity. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al., one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone

marrow damage.

In response to this rejection, Applicants contend that Kennel et al., as a primary reference, specifically state that although HEHA-chelated actinium 225 coupled to a targeting antibody may deliver a tumorical dose to the lung, the radiologic side effects due to release of daughter alpha's limits the effectiveness of therapy. Kennel also state that they know of no conventional chelate that would withstand the energy release. However, Applicants contend that Kennel is silent about any way to reduce the radiologic side effects attributable to the release of alpha particles from the Ac225 and the daughters. Moreover, Applicants contend that combining the teachings of Satoh et al., Jones et al., Schilcher et al. or Nair et al. with Kennel et al can not remedy these deficiencies. In particular, Applicants contend that none of the references teach an Ac225-Mab conjugate nor administering the same as a radioimmunotherapeutic against a pathophysiological condition. Also, Applicants contend that, contrary to the Examiner statement, Schilcher et al .doe not teach or suggest using a diuretic to prevent nephrotoxicity from a radiometal. On the contrary Applicants contend that Schilcher et al .only states that cumulative nephrotoxicity from cisplatin chemotherapy was prevented by treatment with the diuretic furosemide, wherein the platinum in cisplatin is not a radiometal. For example, Applicants contend that the mechanism of action in causing nephrotoxicity of cisplatin and the emitted alpha particles from Fr221 and Bi213 are very different, particularly as the francium and bismuth per se, unlike platinum in cisplatin, are not causing the toxicity. Thus, Applicants contend that a person having ordinary skill in the art would not extrapolate from a nonradiometal to a radiometal with any reasonable expectation of success. Additionally, Applicants Assert that Nair et al .neither teach or suggest that diuretics are radioprotector compounds and further, amended claim 1 and 49 no longer recite a combination. As such, Applicants contend that the prior art does not teach that diuretics are useful to prevent nephrotoxicity from radiometals.

These arguments have been carefully considered, but are not found persuasive.

First, it appears that Applicants are arguing the references individually, but does not account for the cited references used in combination. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. Moreover, the test for obviousness is not whether the features of a

secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Secondly, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, the Examiner recognizes that Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate, wherein the radiotoxicity associated with 213Bi accumulation in the kidneys limits the effectiveness of the therapy, while Satoh et al., Jones et al. and Schilcher et al. each teach agents which are effective at reducing toxicities associated with radiotherapies . As such, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al., one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage. Thirdly, regarding Applicants specific assertion to Schilcher et al., the Examiner acknowledges and does not dispute Applicants arguments that the platinum in cisplatin is not a radiometal. However, the Examiner recognizes that Applicants arguments pertaining to the differing mechanisms of action are moot with out some type of evidence to suggest that indeed the mechanisms of causing nephrotoxicity are different and that furosemide administration would result in a different effect. Applicants are reminded that a reasonable expectation of success, not an

absolute expectation of success is required in obviousness. Lastly, in regards to Applicants assertions pertaining to the claims, the Examiner acknowledges that independent claims 1 and 40 have been amended to remove the administration of a competitive metal blocker and chelator. However, the Examiner recognizes that the claims recite the transitional phrase "comprising". As such, the transitional phrase comprising allows for additional material and/or steps to be added.

Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*), and Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) and in further view of Nair et al. (J. Radiat. Res. 2001; 42: 21-37).

Scheinberg et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 2, paragraph 0016). With regards to the cancer, the publication teaches (page 4, paragraph 0037) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the publication teaches (page 2, paragraph 0017) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 2, paragraph 0021) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the toxicity of ^{225}Ac constructs, wherein histological analysis of deceased mice showed gastrointestinal mucosal sloughing and bond marrow hyplasia, consistent with severe radiotoxicity (column 8, paragraph 0097).

Scheinberg et al. does not explicitly teach administering a competitive metal blocker such as bismuth subnitrate, a chelator such as DMPS or a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ–ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage by γ-ray irradiation without compromising the tumor-reducing effect

(page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Nair et al. teach radioprotector in radiotherapy. In particular, the reference teaches that while acute toxicity has been a main reason for radioprotectors failure in clinical applications, the use of nontoxic amounts of several radioprotectors having a different mechanism of action can overcome the problems associated with their toxicity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention to combine the teachings of the references so as to modify the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al.. One would have been motivated to do so because each of the references teach that the agents are effective at reducing toxicities associated

with radiotherapies. Moreover, as taught by Nair et al., combining several radioprotectors having a different mechanism of action can overcome problems associated with radioprotector toxicity. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Kennel et al. to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al., one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage.

In response to this rejection, Applicants reiterate their arguments above. Hence, the Examiner's response from above in incorporated herein.

Claims 1-2, 4-5, 8-12, 49, 51-53 and 58-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDevitt et al. (Science 2001; 294: 1537-1540, *of record*) in view of Satoh et al. (Eur. J. Cancer Clin Oncol. 1989; 25: 1727-1731), Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113, *of record*), and Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60, *of record*) and in further view of Nair et al. (J. Radiat. Res. 2001; 42: 21-37).

McDevitt et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 1537, Abstract). With regards to the cancer, the reference teaches (page 1537, Abstract) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the reference teaches (page 1538, 1st column, 2nd full paragraph) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 1538, 1st column, 2nd full paragraph) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs (page 1538, Figure 1B).

McDevitt et al. does not explicitly teach administering a diuretic such as furosemide, a dithiol chelate and a metal blocker such as bismuth subnitrate in combination with the ^{225}Ac conjugate.

Satoh et al. teach the effects of preinduction of metallotheionein (MT) by bismuth subnitrate (BSN) on the adverse effects and antitumor activity of γ–ray irradiation in mice (abstract). In particular, the reference teaches that oral administration of BSN markedly reduced the lethal effects and bone marrow damage by γ-ray irradiation without compromising the tumor-reducing effect (page 1730, 1st column, last paragraph). As such, Satoh et al. teach that bismuth subnitrate pretreatment is an effective method for protection against side-effects in radiotherapy (abstract).

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Nair et al. teach radioprotector in radiotherapy. In particular, the reference teaches that while acute toxicity has been a main reason for radioprotectors failure in clinical applications, the use of nontoxic amounts of several radioprotectors having a different mechanism of action can overcome the problems associated with their toxicity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention to combine the teachings of the references so as to modify the method taught by McDevitt to

include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al.. One would have been motivated to do so because each of the references teach that the agents are effective at reducing toxicities associated with radiotherapies. Moreover, as taught by Nair et al., combining several radioprotectors having a different mechanism of action can overcome problems associated with radioprotector toxicity. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by McDevitt to include administration of a metal blocker such as bismuth subnitrate, a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and a diuretic such as furosemide in view of the teachings of Satoh et al., Jones et al. and Schilcher et al., one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney, as well as bone marrow damage.

In response to this rejection, Applicants reiterate their arguments above. Hence, the Examiner's response from above in incorporated herein.

Therefore, No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Primary Examiner
Art Unit 1642

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642